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(54) Title: DRUG CONJUGATES AND THEIR USE FOR TREATING CANCER, AN AUTOIMMUNE DISEASE OR AN INFECTIOUS DISEASE

(57) Abstract: Drug-Linker-Ligand Conjugates are disclosed in which a Drug is linked to a Ligand via a peptide-based Linker unit. In one embodiment, the Ligand is an Antibody. Drug-Linker compounds and Drug compounds are also disclosed. Methods for treating cancer, an autoimmune disease or an infectious disease using the compounds and compositions of the invention are also disclosed.

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AMENDED CLAIMS
received by the International Bureau on16 June 2004 :
claims 1,5, 7 are amended, 93-119 are added, claims 2-4,6 and 8-92 are unchanged.

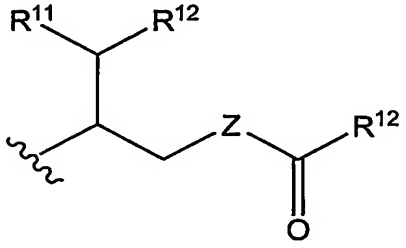
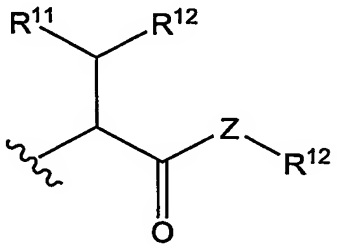
R^6 is selected from -H and -C_1-C_8 alkyl;

R^7 is selected from -H, -C_1-C_8 alkyl, -C_3-C_8 carbocycle, -O-(C_1-C_8 alkyl), -aryl, -C_1-C_8 alkyl-aryl, -C_1-C_8 alkyl-(C_3-C_8 carbocycle), -C_3-C_8 heterocycle and -C_1-C_8 alkyl-(C_3-C_8 heterocycle);

each R^8 is independently selected from -H, -OH, -C_1-C_8 alkyl, -C_3-C_8 carbocycle and -O-(C_1-C_8 alkyl);

R^9 is selected from -H and -C_1-C_8 alkyl;

R^{10} is selected from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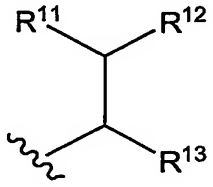

;

Z is -O-, -S-, -NH- or -N(R^{14})-;

R^{11} is selected from -H, -OH, -NH_2, -NHR^{14}, -N(R^{14})$_2$, -C_1-C_8 alkyl, -C_3-C_8 carbocycle, -O-(C_1-C_8 alkyl), -aryl, -C_1-C_8 alkyl-aryl, -C_1-C_8 alkyl-(C_3-C_8 carbocycle), -C_3-C_8 heterocycle and -C_1-C_8 alkyl-(C_3-C_8 heterocycle); or R^{11} is an oxygen atom which forms a carbonyl unit (C=O) with the carbon atom to which it is attached and a hydrogen atom on this carbon atom is replaced by one of the bonds in the (C=O) double bond;

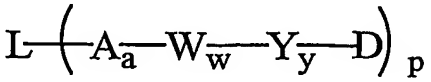
each R^{12} is independently selected from -aryl and -C_3-C_8 heterocycle;

R^{13} is selected from -H, -OH, -NH_2, -NHR^{14}, -N(R^{14})$_2$, -C_1-C_8 alkyl, -C_3-C_8 carbocycle, -O-(C_1-C_8 alkyl), -aryl, -C_1-C_8 alkyl-aryl, -C_1-C_8 alkyl-(C_3-C_8 carbocycle), C_3-C_8 heterocycle and -C_1-$_8$ alkyl-(C_3-C_8 heterocycle); and

Each R^{14} is independently -H or -C_1-C_8 alkyl.

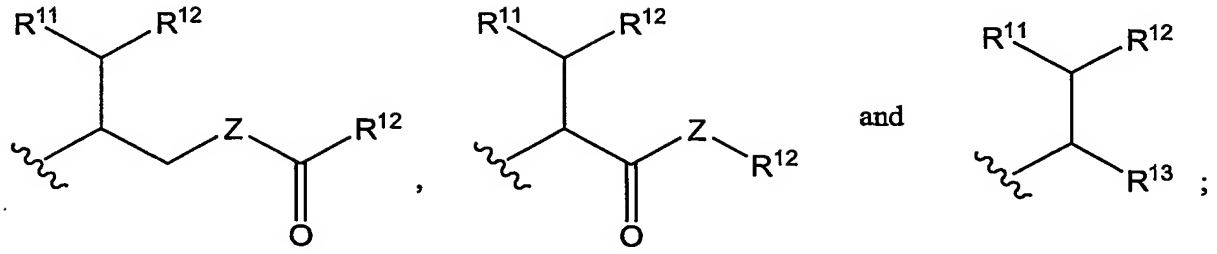
2. The compound of claim 1 wherein w is an integer ranging from 2 to 12.

3. A compound of the formula Ib:



Ib

or a pharmaceutically acceptable salt or solvate thereof



Z is -O-, -S-, -NH- or -N(R^{14})-;

R^{11} is selected from -H, -OH, -NH_2, -NHR^{14}, -$N(R^{14})_2$, -C_1-C_8 alkyl, -C_3-C_8 carbocycle, -O-(C_1-C_8 alkyl), -aryl, -C_1-C_8 alkyl-aryl, -C_1-C_8 alkyl-(C_3-C_8 carbocycle), -C_3-C_8 heterocycle and -C_1-C_8 alkyl-(C_3-C_8 heterocycle); or R^{11} is an oxygen atom which forms a carbonyl unit (C=O) with the carbon atom to which it is attached and a hydrogen atom on this carbon atom is replaced by one of the bonds in the (C=O) double bond;

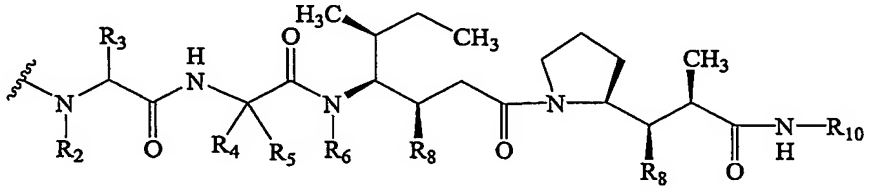
each R^{12} is independently selected from -aryl and -C_3-C_8 heterocycle;

R^{13} is selected from -H, -OH, -NH_2, -NHR^{14}, -$N(R^{14})_2$, -C_1-C_8 alkyl, -C_3-C_8 carbocycle, -O-(C_1-C_8 alkoxy), -aryl, -C_1-C_8 alkyl-aryl, -C_1-C_8 alkyl-(C_3-C_8 carbocycle), C_3-C_8 heterocycle and -C_1-C_8 alkyl-(C_3-C_8 heterocycle); and

each R^{14} is independently -H or -C_1-C_8 alkyl.

6. The compound of claim 5 wherein w is an integer ranging from 2 to 12.

7. A compound or a pharmaceutically acceptable salt or solvate of the compound of claim 1 where -D is a Drug unit having the structure



or a pharmaceutically acceptable salt or solvate thereof,

wherein, independently at each location:

R^2 is selected from -H and -methyl;

R^3 is selected from -H, -methyl, and -isopropyl;

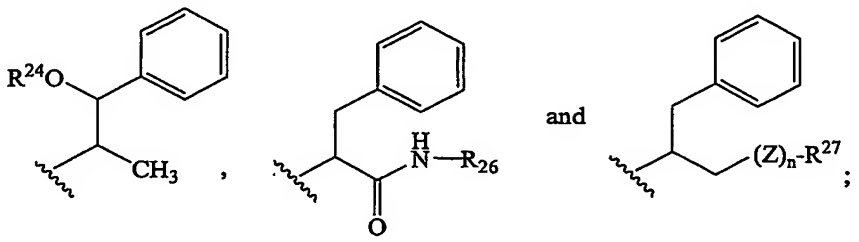
R^4 is selected from -H and -methyl; R^5 is selected from -isopropyl, -isobutyl, -sec-butyl, -methyl and -t-butyl or R^4 and R^5 join, have the formula – $(CR^aR^b)_n$- where R^a and R^b are independently selected from -H, -C_1-C_8 alkyl, and -C_3-C_8 carbocycle, and n is

selected from 2, 3, 4, 5 and 6, and form a ring with the carbon atom to which they are attached;

R^6 is selected from -H and -methyl;

each R^8 is independently selected from -OH, -methoxy and -ethoxy;

R^{10} is selected from



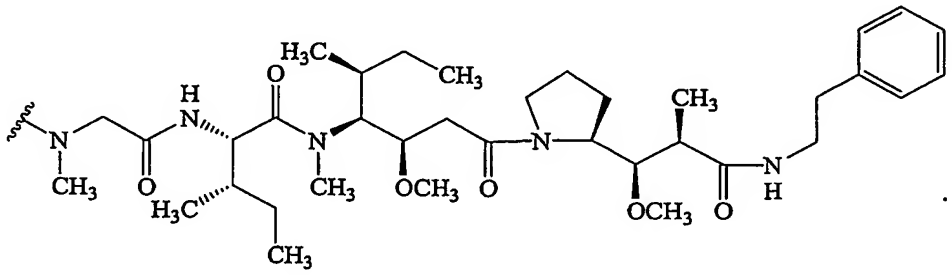
R^{24} is selected from H and $-C(O)R^{25}-$; wherein R^{25} is selected from $-C_1-C_8$ alkyl, $-C_3-C_8$ carbocycle, -aryl, $-C_1-C_8$ alkyl-aryl, $-C_1-C_8$ alkyl-(C_3-C_8 carbocycle), $-C_3-C_8$ heterocycle and $-C_1-C_8$ alkyl-(C_3-C_8 heterocycle);

Z is -O-, -NH-, -OC(O)-, -NHC(O)-, $-NR^{28}C(O)-$; where R^{28} is selected from -H and $-C_1-C_8$ alkyl;

n is 0 or 1; and

R^{27} is selected from -H, $-N_3$, $-C_1-C_8$ alkyl, $-C_3-C_8$ carbocycle, -aryl, $-C_1-C_8$ alkyl-aryl, $-C_1-C_8$ alkyl-(C_3-C_8 carbocycle), $-C_3-C_8$ heterocycle and $-C_1-C_8$ alkyl-(C_3-C_8 heterocycle) when n is 0; and R^{27} is selected from -H, $-C_1-C_8$ alkyl, $-C_3-C_8$ carbocycle, -aryl, $-C_1-C_8$ alkyl-aryl, $-C_1-C_8$ alkyl-(C_3-C_8 carbocycle), $-C_3-C_8$ heterocycle and $-C_1-C_8$ alkyl-(C_3-C_8 heterocycle) when n is 1.

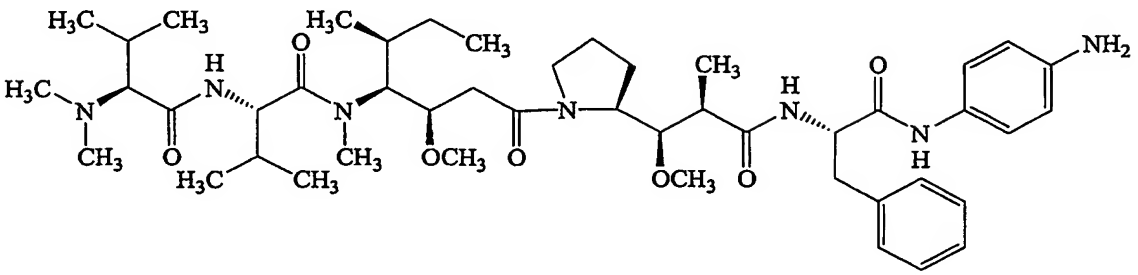
8. A compound or a pharmaceutically acceptable salt or solvate of the compound of claim 1 where -D is a Drug unit having the structure



9. A compound or a pharmaceutically acceptable salt or solvate of the compound of claim 1 where -D is a Drug unit having the structure

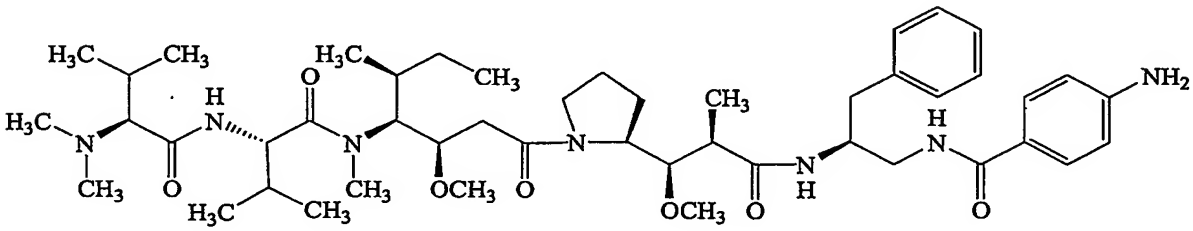
or a pharmaceutically acceptable salt or solvate thereof.

90. A compound having the structure



or a pharmaceutically acceptable salt or solvate thereof.

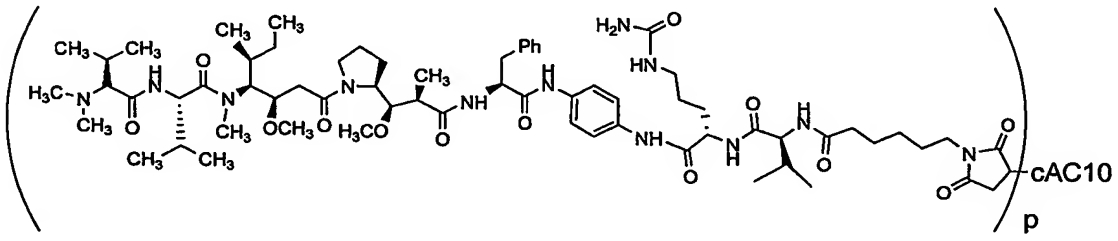
91. A compound having the structure



or a pharmaceutically acceptable salt or solvate thereof.

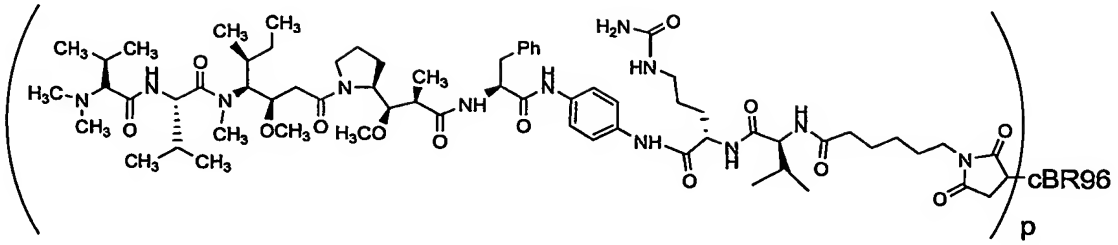
92. The compound or a pharmaceutically acceptable salt or solvate thereof of any one of claims 1, 3, 5, 32, 34, 35, 36, 37, 38, 43 or 44, in an isolated or a purified form.

93. A compound having the structure



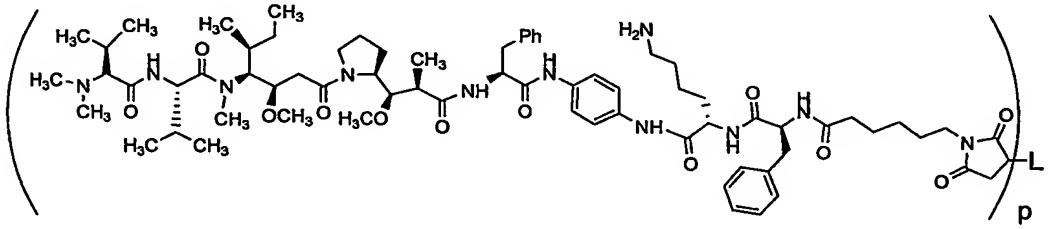
or a pharmaceutically acceptable salt or solvate thereof, where p ranges from about 7 to about 9.

94. A compound having the structure



or a pharmaceutically acceptable salt or solvate thereof, where p ranges from about 7 to about 9

95. A compound having the structure

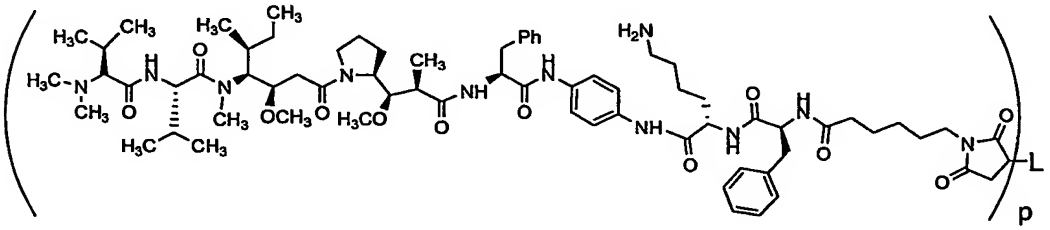


or a pharmaceutically acceptable salt or solvate thereof,

where p ranges from about 7 to about 9; and L is an anti-CD20 antibody.

96. The compound of claim 95 wherein L is rituximab.

97. A compound having the structure

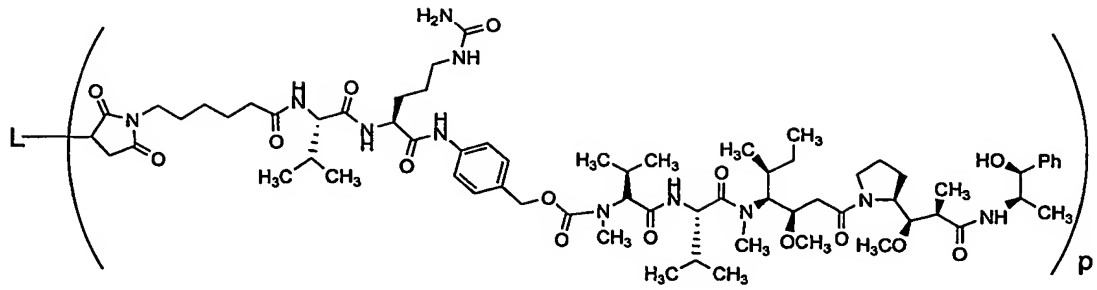


or a pharmaceutically acceptable salt or solvate thereof,

where p ranges from about 7 to about 9; and L is an anti-CD40 antibody.

98. The compound of claim 97 wherein L is S2C6.

99. A compound having the structure

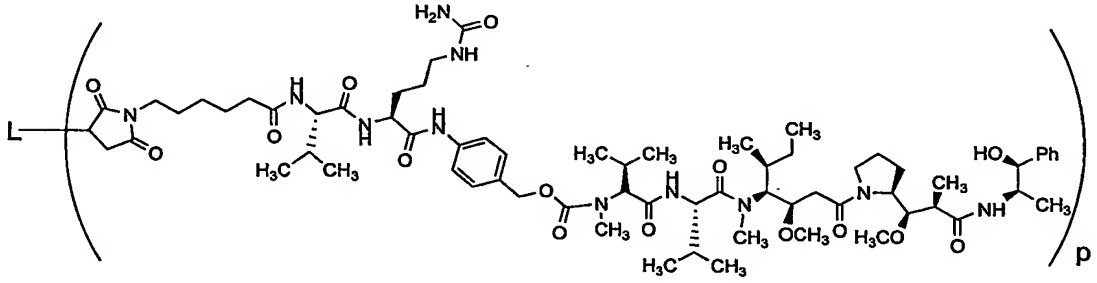


or a pharmaceutically acceptable salt or solvate thereof,

where p ranges from about 7 to about 9; and L is an anti-CD20 antibody.

100. The compound of claim 99 wherein L is rituximab.

101. A compound having the structure

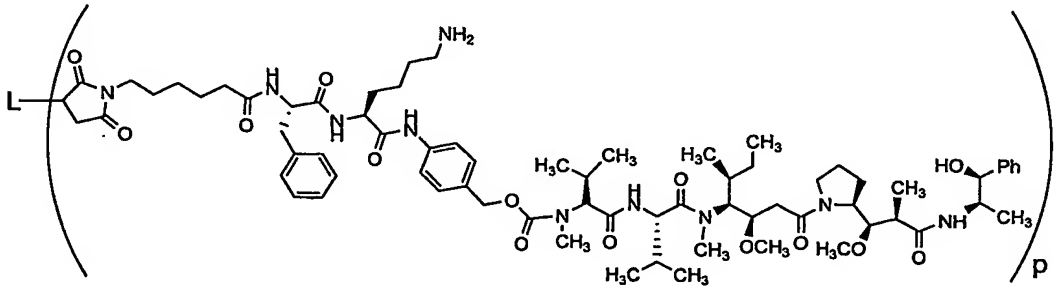


or a pharmaceutically acceptable salt or solvate thereof,

where p ranges from about 7 to about 9; and L is an anti-CD40 antibody.

102. The compound of claim 101 wherein L is S2C6.

103. A compound having the structure

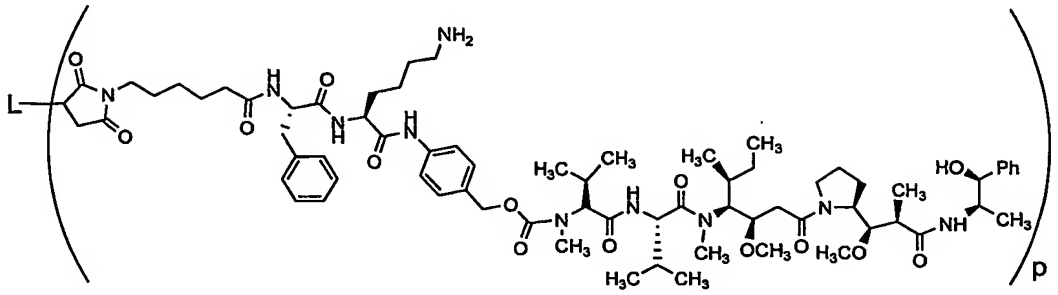


or a pharmaceutically acceptable salt or solvate thereof,

where p ranges from about 7 to about 9; and L is an anti-CD20 antibody.

104. The compound of claim 103 wherein L is rituximab.

105. A compound having the structure

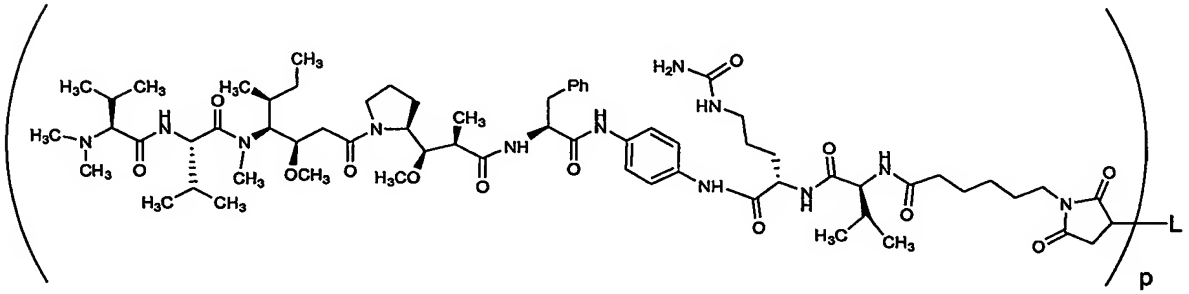


or a pharmaceutically acceptable salt or solvate thereof,

where p ranges from about 7 to about 9; and L is an anti-CD40 antibody.

106. The compound of claim 105 wherein L is S2C6.

107. A compound having the structure

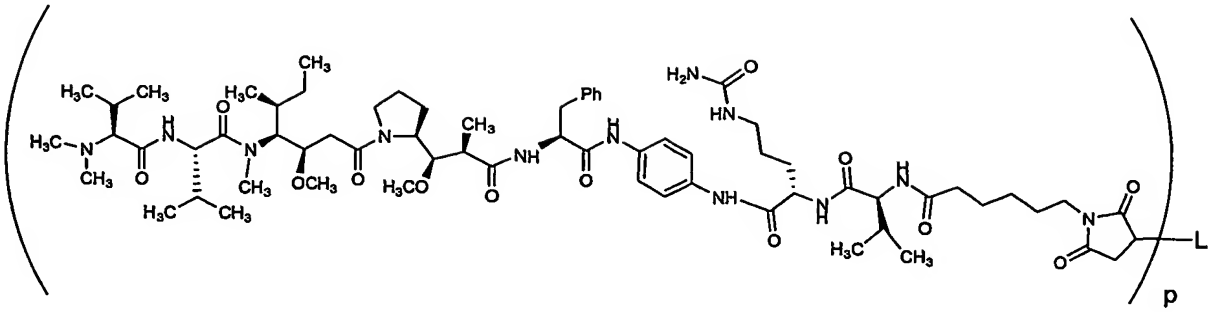


or a pharmaceutically acceptable salt or solvate thereof,

where p ranges from about 7 to about 9; and L is an anti-CD20 antibody.

108. The compound of claim 107 wherein L is rituximab.

109. A compound having the structure



or a pharmaceutically acceptable salt or solvate thereof,

where p ranges from about 7 to about 9; and L is an anti-CD40 antibody.

110. The compound of claim 109 wherein L is S2C6.

111. A composition comprising an effective amount of a compound or a pharmaceutically acceptable salt or solvate thereof of any one of claims 77-91, 93-95, 97, 99, 101, 103, 105, 107 and 109 and a pharmaceutically acceptable carrier or vehicle.

112. A method for killing or inhibiting the multiplication of a tumor cell or cancer cell comprising administering to an animal in need thereof a therapeutically effective amount of a compound or a pharmaceutically acceptable salt or solvate thereof of any one of claims 77-91, 93-95, 97, 99, 101, 103, 105, 107 and 109.

113. A method for treating cancer, comprising administering to an animal in need thereof an effective amount of a compound or a pharmaceutically acceptable salt or solvate of the compound of any one of claims 77-91, 93-95, 97, 99, 101, 103, 105, 107 and 109.

114. A method for treating an autoimmune disease, comprising administering to an animal in need thereof an effective amount of a compound or a pharmaceutically acceptable salt or solvate of the compound of any one of claims 77-91, 93-95, 97, 99, 101, 103, 105, 107 and 109.

115. A method for treating an infectious disease, comprising administering to an animal in need thereof an effective amount of a compound or a pharmaceutically acceptable salt or solvate of the compound of any one of claims 77-91, 93-95, 97, 99, 101, 103, 105, 107 and 109.

116. The method of claim 113 further comprising administering to the animal an effective amount of an anticancer agent.

117. The method of claim 114 further comprising administering to the animal an effective amount of an immunosuppressant agent.

118. The method of claim 115 further comprising administering to the animal an effective amount of an anti-infectious agent.

119. The compound or a pharmaceutically acceptable salt or solvate thereof of any one of claims 77-91, 93-95, 97, 99, 101, 103, 105, 107 and 109, in an isolated or a purified form.